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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/551,482	WESTON-DAVIES, WYNNE	
	Examiner	Art Unit	
	Prema M. Mertz	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *7/17/08, 12/5/08*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5 and 11-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 11-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/31/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group II (claims 1-9, species of disease: ARDS) in the reply filed on 7/17/08 is acknowledged. The traversal is on the grounds that the restriction is improper since the Groups are unified by a single general inventive concept and that the unifying feature of the instant claims is a method of treating a disease condition mediated by neutrophil cells that calls for administering EV 131 while the WO 0115719 application does not disclose a method of treating a neutrophil-mediated disease. This argument is not found persuasive because the reference teaches a method of using histacalin proteins (EV 131) for the treatment of allergic conjunctivitis in which white blood cells neutrophils are involved (See page 3, line 25; page 4, line 32; page 7, column 2; examples 1,2). Therefore treating a disease involving neutrophils is implicit and inherent in the method of the prior art reference meeting the limitations of the claims of Group I. Furthermore, original claim 3, line 16, which is dependent on claim 1, recites "severe allergic conjunctivitis" as one of the diseases mediated by neutrophils. Therefore, Applicants arguments are moot with respect to the prior art not disclosing a method of treating a neutrophil-mediated disease.

The test for propriety of a restriction is not whether the inventions are related but rather whether they are distinct and whether it would impose a burden on the examiner to search and examine multiple inventions in a single invention. The inventions are distinct because a search of the literature for a method of treating an autoimmune disease, would not necessarily be expected to reveal art for a method of treating an allergic disease, which searches are extensive requiring

separate searches and treatment of different patient populations which would be unduly burdensome.

Having shown that these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different and recognized divergent subject matter as defined by MPEP § 808.02, the Examiner has *prima facie* shown a serious burden of search (see MPEP § 803). Therefore, an initial requirement of restriction for examination purposes as indicated is proper.

The Groups as delineated in the restriction requirement 4/17/08 are patentably distinct one from the other such that each invention could, by itself, in principle, support its own separate patent (as shown by the arguments put forth in the written restriction requirement).

The requirement is still deemed proper and is therefore made FINAL.

Furthermore, Applicants supplemental amendment submitted 12/5/08 renders the traversal of the restriction moot. Amended claims 1-5 and new claims 11-15 (12/5/08) are pending and under consideration by the Examiner and will be examined with respect to the elected species ARDS.

Claim Rejections - 35 USC § 112, first paragraph, scope of enablement

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2a. Claims 1-5, 11-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating a bronchoconstrictive disease, ARDS, by administering EV131 protein comprising the amino acid sequence set forth in SEQ ID NO:6, does not reasonably provide enablement for a method as recited in claim 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification delimits the instant EV131 protein by reference to specific amino acid arrays as set forth in SEQ ID NO:6, however, in the claims, the protein is defined by reference to the abbreviation EV131, wherein the abbreviation itself does not represent any distinguishing information concerning the disclosed protein. Moreover because EV131 does not inherently correspond to any particular protein, claims that lack the recitation of structural properties encompass subject matter not supported by the instant specification. Molecules that are embraced by the claims are not adequately supported by the instant specification because the specification provides no guidance for how to make such molecules nor are examples provided as to how these ,molecules would be identified commensurate with the breadth of the claims. In the absence of an appropriate structural and/or functional reference, a person of ordinary skill in the art would be unable to make and use the molecules embraced by the claims without undue experimentation because one could not distinguish the proteins envisaged by the specification and those which are unrelated.

The claims are drawn very broadly to methods of treating all bronchoconstrictive diseases ranging from ARDS to cystic fibrosis. However, other than the inhibition of bronchoconstrictive disease induced by endotoxin by administering EV131 of amino acid sequence set forth in SEQ

ID NO:6, the specification fails to provide any guidance for the successful treatment of all the disparate bronchoconstrictive diseases.

The specification delimits the instant method to administering EV131 and fragments thereof. However, the specification, page 5, lines 26-29, to page 6, lines 1-5, recites:

"Particularly preferred is the protein referred to in WO97/44451 as FS-I-IBP2 (also known as EV131), or a variant or an active fragment thereof as recited in (a), (b), (c), (d) or (e) above. This protein binds to histamine with high affinity and specificity and is shown herein to be effective in an animal model of neutrophil-mediated disease.

Active fragments according to (e) above should comprise at least n consecutive amino acids from the sequence of the protein responsible for binding to histamine find, depending on the particular sequence, n preferably is 7 or more (for example, 8, 10, 12, 14, 16, 18, 20, 50, 100, 150, 200, 250 or more). Such fragments may be "free-standing", i.e. not part of or fused to other amino acids or polypeptides, or they may be comprised within a larger polypeptide of which they form a part or region. When comprised within a larger polypeptide, the fragment of the invention most preferably forms a single continuous region. Additionally, several fragments may be comprised within a single larger polypeptide."

The specification is non-enabling for a method of administering a fragment of 7 amino acids as encompassed by the scope of the claims. Claim 1, for example, is a single means claim (M.P.E.P. 2164.08(a)). In In re Hyatt, 708 F.2d 712, 218 USPQ 195 (Fed. Cir. 1983), the Courts

have held that: A single means claim, i.e. where a means recitation does not appear in combination with another recited element of means, is subject to an undue breadth rejection under 35 U.S.C. 112, first paragraph. (A single means claim which covered every conceivable means for achieving the stated purpose was held nonenabling for the scope of the claim because the specification disclosed at most only those means known to the inventor). Since no material limitations for "EV131" have been recited in the claim and only a biological activity has been recited, the claim encompasses every conceivable structure (means) for achieving the stated property (result), a fact situation comparable to Hyatt. Therefore, in the absence of the recitation of structural limitations in the claim, not only proteins, such as antibodies against histamine, but also all other substances, which bind to histamine, are encompassed by the scope of the claim. The claimed invention encompasses a method of administering compositions not envisioned or described in the specification, and neither does the specification disclose how these compositions can be distinguished from each other. The specification only enables a method of administering EV131 polypeptide of amino acid sequence set forth in SEQ ID NO:6, this polypeptide having specific characteristics and properties. These properties may differ structurally, chemically and physically from other known proteins. By application of the factors set forth in Ex parte Forman (230 USPQ 546 (Bd. Pat. App. & Int. 1986), and reiterated in In re Wands (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)), which include (1) quantity of experimentation, (2) guidance presented, (3) the predictability of the art, and (4) the breadth of the claims, in the instant application, the quantity of experimentation to determine which other substances are encompassed by the scope of the claims is practically infinite and the guidance provided in the specification very little, thereby rendering the results of the methods taught in the specification

unpredictable (see pages 12-13). Therefore, it would require undue experimentation to determine which other substances having histamine binding activity activity, would be encompassed by the scope of the method claims. The disclosure of these two polypeptides is clearly insufficient support under the first paragraph of 35 U.S.C. 112 for claims, which encompass a method of administering every and all CD40 receptor inducers and promoters of T-cell expansion, including analogs of such. In In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970), the Courts have held that:

"Inventor should be allowed to dominate future patentable inventions of others where those inventions were based in some way on his teachings, since some improvements while unobvious from his teachings, are still within his contribution, since improvement was made possible by his work; however, he must not be permitted to achieve this dominance by claims which are insufficiently supported and hence, not in compliance with first paragraph of 35 U.S.C. 112; that paragraph requires that the scope of the claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific law; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved."

Furthermore, the amount of embodiments corresponding to the desirable compositions, may be innumerable, and the enabled embodiments amount to only one. Therefore, there are

substantial scientific reasons to doubt the scope of enablement, as set forth above. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. The specification does not describe administering any other polypeptides other than EV131 protein of amino acid sequence set forth in SEQ ID NO:6, and since it is deemed to constitute undue experimentation to determine all the others, the disclosure is not commensurate with the scope of the claims. It is suggested that by employing conventional claim language, the method claims be amended to include the specific polypeptides supported by the instant specification.

Furthermore, claims 1 and 11 as recited encompass a method of treating every and all bronchoconstrictive states known to man, including cystic fibrosis.

In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) states, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." "The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling" (MPEP 2164.03). The MPEP further states that physiological activity can be considered inherently unpredictable. Given the inherent unpredictability of physiological activity, which would include biological processes, i.e., methods of treatment, a certain amount of enablement beyond mere assertion must be required.

The CAFC decision (Genentech Inc. v. Novo Nordisk, 42 USPQ2d 1001, 1997) expressly states that:

"When there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement".

If Applicants will kindly review page 1404 of In re Wands, they will find that the factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

In the instant case, the method of treating cystic fibrosis, is very different from a method of treating ARDS. Furthermore, the limited results presented for bronchoconstriction induced by endotoxin, are not sufficient to enable the breadth of the claims and are not predictive of in vivo efficacy for treatment of all bronchoconstrictive conditions. The treatment of cystic fibrosis has been the subject of intense study for the past several decades. Many promising treatments and therapies have been identified via in vitro experiments, and have not lived up to expectations when tested in vivo. In fact, the number of such treatments, which have failed to live up to their

promise exceeds those, which have been performed as hoped by orders of magnitude. The effectivity of the claimed method against one type of bronchoconstrictive disease may be different from another specific type depending on the developmental stage of the disease. The skilled artisan would have to undergo undue experimentation to determine if there is a therapeutically effective amount of the claimed EV131 products to be utilized for treating the various types of conditions. Thus, it would require undue experimentation on the part of the skilled artisan to use the claimed method for treated as recited, in the absence of sufficient information to predict the results with an adequate degree of certainty. In view of this unpredictability in treatment, the recitation of "bronchoconstrictive disease" in claim 1, is not commensurate with the scope of the specification. Given the breadth of claim 1 in light of the predictability of the art as determined by the number of working examples, the level of skill of the artisan, and the guidance provided in the instant specification and the prior art of record, it would require undue experimentation for one of skill in the art to practice the claimed invention.

With respect to claim 1(b), the specification is not enabling for "a fragment of the EV131 protein that retains a biological function of EV131... ", since no reasonable expectation of success and no working example of biologically active fragments of the protein comprising the amino acid sequence shown in SEQ ID NO:6, have been provided in the specification such that fragments of the protein or substitution, deletion, or addition of a single amino acid residue would enable a protein of the biological characteristics of the secreted protein. It is also asserted that if applicants were to randomly begin making fragments, the success rate, i.e. those which would have any asserted biological activity, would be low. There is little to no guidance as to which of these fragments would possess any biological activity. The specification provides only

primary sequence data (i.e. SEQ ID NO:6). Further, if the biological activity belongs to the fragment of the amino acid sequence of SEQ ID NO:6, the specification does not teach either which portion or which amino acids of the sequence are necessary for activity. Additionally, one would expect that fragmentation of a 190 amino acid protein would abolish any type of activity because activity is determined not only by primary sequence, but also three-dimensional structure, as for example, is the case for the ligand binding site of a receptor or for the catalytic site of an enzyme. For these reasons, it would require undue experimentation to determine if the fragment has biological activity, and therefore, to make and use the claimed invention the experimentation would be undue.

Claim rejections-35 U.S.C. 112, second paragraph

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-5, 11-15, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is rejected as vague and indefinite for several reasons.

Claim 1 recites the limitation "the EV131 protein" in line 5. There is insufficient antecedent basis for this limitation in the claim.

Claim 1, line 5, is vague and indefinite because it recites “EV131”. The metes and bounds of this term are unclear.

Similarly, claim 11, line 4, is vague and indefinite because it recites "EV131". The metes and bounds of this term are unclear.

Claim 1, line 1, is improper because it recites "disease condition", which recitation is redundant.

Similarly, claim 3, line 2, is improper because it recites "disease condition", which recitation is redundant.

Claim 11, line 1, is improper because it recites "disease condition", which recitation is redundant.

Claim 15, lines 1-2, is improper because it recites "disease condition", which recitation is redundant.

Claims 2, 4-5, 12-14, are rejected as vague and indefinite insofar as they depend on the above rejected claims for their limitations.

Claim rejections-35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4a. Claims 1-2, 4-5, 11-14, are rejected under 35 U.S.C. § 102(b) as being anticipated by WO 96/38481.

The reference describes histamine binding compounds, specifically FS-HBP2 (EV131), capable of binding to histamine with a dissociation constant of less than 10^{-7} M and the use of the histamine binding proteins as anti-inflammatory drugs and the treatment of allergies such as asthma which is a bronchoconstrictive disease (see page 1, lines 22-28; claims 1-44; page 12, lines 14-16; page 13, lines 15-26). The reference also discloses fusion proteins comprising the EV131 protein (see page 10, lines 24-30; page 24, lines30-32 and page 25, lines 1-3). Furthermore, the reference discloses a fusion protein comprising EV131 fused to a label, toxin or bioactive molecule for the purpose of detection, expression, separation or purification of the histamine binding compound (see page 11, lines 2-8).

Therefore, the method disclosed in reference meets the limitations recited in claims 1-2, 4-5 and 11-14.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

5a. Claims 1-5, 11-15, are rejected under 35 U.S.C. § 103 as being unpatentable over WO 99/27104 A .

The disclosure of the reference is set forth above in paragraph 4a. However, the reference is silent about the treatment of bronchoconstrictive diseases selected from the group consisting of adult respiratory distress syndrome (ARDS); infant respiratory distress syndrome (IRDS); severe acute respiratory syndrome (SARS); chronic obstructive airways disease (COPD); cystic fibrosis; and ventilator induced lung injury (VILI); by administering the histamine binding compound, EV131 (FS-HBP2).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the instant invention was made to administer the histamine binding compound EV131 to patients with bronchoconstrictive disease such as ARDS (the elected species) because the reference teaches that histamine regulates inflammatory processes (page 1, lines 16-21). Furthermore, it is

well known in the art at the time of the invention that histamine is a vasoconstrictor and airway construction can be inhibited by administering an anti-histamine or histamine antagonist such as histamine binding compounds (also, see page 1, lines 16-21 of reference). To have administered the EV131 protein to a patient for the treatment of bronchoconstrictive disease such as ARDS based on the knowledge in the art, at the time that the instant invention was made, would have been *prima facie* obvious to an artisan in light of the WO 99/27104 reference.

Conclusion

No claim is allowed.

Claims 1-5, 11-15, are rejected.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Prema Mertz whose telephone number is (571) 272-0876. The examiner can normally be reached on Monday-Friday from 7:00AM to 3:30PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, can be reached on (571) 272-0835.

Official papers filed by fax should be directed to (571) 273-8300. Faxed draft or informal communications with the examiner should be directed to (571) 273-0876.

Information regarding the status of an application may be obtained from the Patent application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Prema Mertz/

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